PCT / IN 04 / 00052

INTELLECTUAL PROPERTY INDIA
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सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 20/06/2003 in respect of Patent Application No. 647/MUM/2003 of SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI – 400 059, MAHARASHTRA, INDIA, AN INDIAN COMPANY.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Dated this 27th day of April 2004.

(N. K. GARG)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 39)

We, **SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA.**

AN INDIAN COMPANY
hereby declare -

(i) that we are in possession of an invention titled **"A PROCESS FOR PREPARATION OF 1-[9'H-CARBAZOL-4'-YLOXY]-3-[{2''-(2''-(METHOXY) PHENOXY)-ETHYL}-AMINO]-PROPAN-2-OL"**

(ii) that the provisional specification relating to this invention is filed with this application.

(iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are

1) MR. CHHABADA VIJAY CHHANGAMAL 2) DR. REHANI RAJEEV BUDHDEV 3) DR. THENNATI RAJAMANNAR; all of SUN PHARMA ADVANCED RESEARCH CENTRE, AKOTA ROAD, AKOTA, BARODA 390020, GUJARAT, INDIA; all Indian nationals.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

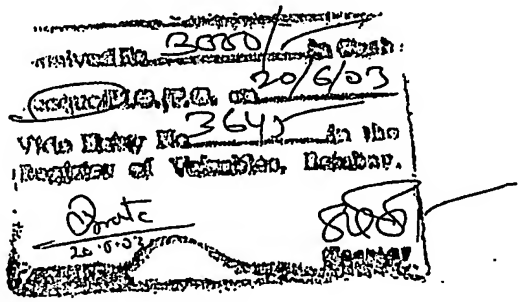
We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

Dr. RATNESH SHRIVASTAVA,
INTELLECTUAL PROPERTY CELL,
SUN PHARMACEUTICAL INDUSTRIES LTD,
ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (E), MUMBAI-400 059, MAHARASHTRA, INDIA,
TELEPHONE NO-28397632, FACSIMILE NO- 28212010.

647/MUM/2003
20/6/2003



FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

PROVISIONAL SPECIFICATION

(See section 10; rule 13)

A PROCESS FOR PREPARATION OF 1-[9'H-CARBAZOL-4'-YLOXY]-3-[{2''-(2''-(METHOXY)PHENOXY)-ETHYL}-AMINO]-PROPAN-2-OL

SUN PHARMACEUTICAL INDUSTRIES LTD.

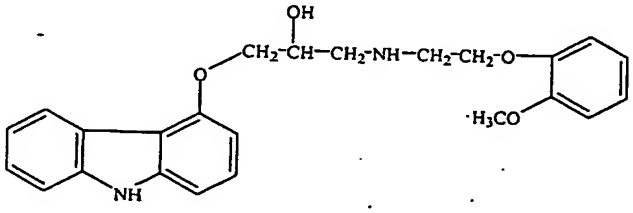
A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA.

The following specification describes the nature of this invention.

A PROCESS FOR PREPARATION OF 1-[9'H-CARBAZOL-4'-YLOXY]-3-[{2''-(2''-(METHOXY)PHENOXY)-ETHYL}-AMINO]-PROPAN-2-OL

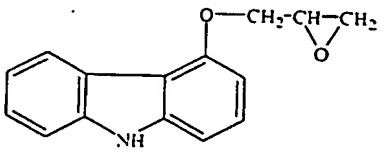
The present invention relates to an improved process for preparation of 1-[9'H-carbazol-4'-yloxy]-3-[{2''-(2''-(methoxy)phenoxy)-ethyl}-amino]-propan-2-ol.

1-[9'H-carbazol-4'-yloxy]-3-[{2''-(2''-(methoxy)phenoxy)-ethyl}-amino]-propan-2-ol, a compound of formula 1, is a well known drug with INN name, carvedilol having antihypertensive effect. Carvedilol is a competitive non-selective β-adrenergic blocking agent with α_1-blocking activity.

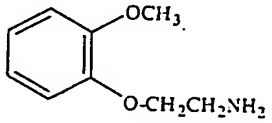


Formula 1

United States Patent No. 4503067 (the '067 patent as referred to hereinafter, Indian reference is not available) in example 2 teaches the preparation of 1-[9'H-carbazol-4'-yloxy]-3-[{2''-(2''-(methoxy)phenoxy)-ethyl}-amino]-propan-2-ol, a compound of formula 1 (carvedilol) in 39% yield, by reaction of 4-(oxiraneylmethoxy)-9H-carbazole, a compound of formula 2 with 2-[2'-(methoxy)-phenoxy]-ethylamine, a compound of formula 3.

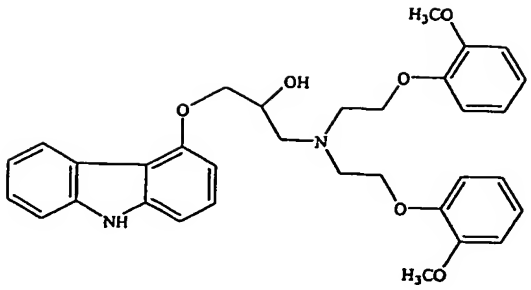


Formula 2



Formula 3

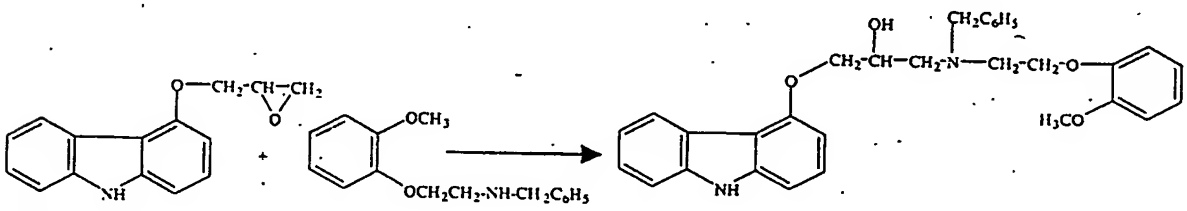
The drawback of the process lies in the fact that along with a compound of formula 1, it also produces a bis-compound of formula 4,



Formula 4

which can not be avoided, making the process uneconomical and unsuitable industrially.

The formation of bis-compound of formula 4 can be avoided by using a secondary amine instead of a primary amine such as compound of formula 3. United States Patent No. 4503067 in example 5 teaches the preparation of 1-[N-{benzyl}-2'-({2''-(methoxy)phenoxy)-ethyl}-amino]-3-[9'''H-carbazol-4'''-yloxy]-propan-2-ol, a compound of formula 6 (referred to as N-benzyl carvedilol herein), which is the penultimate intermediate for preparation of carvedilol, by reaction of 4-(oxiraneylmethoxy)-9H-carbazole, a compound of formula 2 with a secondary amine, viz. N-2-[2'-(methoxy)-phenoxy]-ethyl]-benzylamine, a compound of formula 5,



Formula 2 **Formula 5** **Formula 6**

in ethylene glycol dimethyl ether solvent. However, the process is not industrially applicable as it does not provide N-benzyl carvedilol in crystalline form directly from the reaction mixture, but requires isolation of N-benzyl carvedilol by column chromatography.

European Patent No. 918055B1 (the '055 patent as referred to herein, Indian equivalent is not available) teaches an improved process for preparation of compound of formula 1

(carvedilol) via the intermediate compound of formula 6 (N-benzyl carvedilol). The compound of formula 6 is prepared by reaction of 4-(oxiraneylmethoxy)-9H-carbazole, a compound of formula 2 with N-2-[2'-(methoxy)-phenoxy]-ethyl]-benzylamine, a compound of formula 5 in a protic organic solvent such as ethanol or isopropanol instead of an aprotic solvent like ethylene glycol dimethyl ether used in the '067 patent. Use of protic organic solvent in place of aprotic solvent obviates column chromatography to isolate the N-benzyl carvedilol in crystalline form by providing the N-benzyl carvedilol in solid form directly from the reaction mixture, which can be isolated and then converted to carvedilol or in-situ converted to carvedilol by subjecting to debenzylation by catalytic hydrogenation. The '055 patent exemplifies in the Comparative Examples, that preparation of compound of formula 6 by reaction of compound of formula 2 with compound of formula 5 in an aprotic solvent like ethyl acetate merely provides 3 % of the desired N-benzyl carvedilol, compound of formula 6, even after carrying out the reaction for 28 hours at reflux temperature.

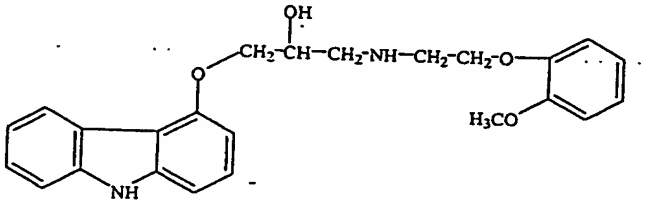
The objective of the present invention is to provide an improved facile process for preparation and purification of compound of formula 1.

We have surprisingly found a facile reaction for preparation of N-benzyl carvedilol, a compound of formula 6 by reaction of compound of formula 2 with a compound of formula 5 in an aprotic organic solvent in presence of catalytic amount of acid compound. The compound of formula 6 can be converted to carvedilol, a compound of formula 1, by subjecting to debenzylation reaction.

In embodiment of the present invention it is found that the reaction of compound of formula 2 with a compound of formula 5 to obtain a compound of formula 6 and debenzylation of the resultant compound of formula 6 to obtain a compound o formula 1 can be carried out in the same organic aprotic solvent.

In embodiment of the present invention it is found that the debenzyaltion of compound of formula 6 can be carried out using significantly lower amount of Pd/C catalyst than hitherto known.

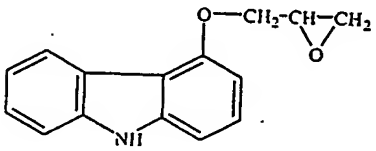
The present invention provides a process for preparation of 1-[9'H-carbazol-4'-yloxy]-3-[{2''-(2''-(methoxy)phenoxy)-ethyl}-amino]-propan-2-ol, a compound of formula 1 or an acid addition salt thereof,



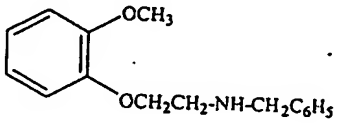
Formula 1

comprising,

a) reacting 4-(oxiraneylmethoxy)-9H-carbazole, a compound of formula 2 with N-2-[2'-(methoxy)-phenoxy]-ethyl]-benzylamine, a compound of formula 5,

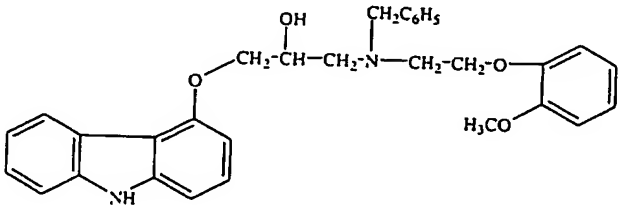


Formula 2



Formula 5

in an aprotic organic solvent in presence of catalytic amount of an acid compound to obtain 1-[N-{benzyl}-2'-({2''-(methoxy)phenoxy)-ethyl}-amino]-3-[9'''H-carbazol-4'''-yloxy]-propan-2-ol, a compound of formula 6,



Formula 6

b) subjecting the resultant compound of formula 6 to debenzylation reaction by catalytic hydrogenation to obtain the compound of formula 1, if desired converting the resultant compound of formula 1 to an acid addition salt thereof.

The present invention provides a facile reaction for preparation of compound of formula 1 (carvedilol), by reaction of compound of formula 2 with a compound of formula 5 in an aprotic organic solvent in presence of catalytic amount of acid compound to form a compound of formula 6 (N-benzyl carvedilol), the compound of formula 6 is converted to the compound of formula 1 by subjecting it to debenzylation reaction.

The aprotic organic solvent like ethers, esters, ketones, amides, nitriles, hydrocarbons, halogenated hydrocarbons, aromatic solvents or mixtures thereof can be used in the process of the present invention. Preferably ethers, esters or amide solvents; more preferably ether or ester solvents may be used. Examples of ethers are cyclic ethers such as dioxane, tetrahydrofuran and the like, acyclic ethers such as dimethoxyethane, disopropylether, methyl-tertbutylether and the like. Examples of ester solvents are ethylacetate, methylacetate and the like.

The acid compound can be an organic acid such as mono or polycarboxylic acids like acetic acid, oxalic acid, citric acid, glutaric acid, succinic acid; a Lewis acid such as $ZnCl_2$, $AlCl_3$, alkali or alkaline earth metal salts such as lithium or magnesium halides and the like; a halocarboxylic acid such as trifluroacetic acid and the like; a substituted or unsubstituted aromatic or heteroaromatic carboxylic acid such as benzoic acid and the like.

In a preferred embodiment of the present invention the aprotic organic solvent is ethyl acetate and the acid compound is an organic acid.

In another preferred embodiment of the present invention the aprotic organic solvent is dioxane and the acid compound is an organic acid.

In another preferred embodiment of the present invention the aprotic organic solvent is dimethoxyethane and the acid compound is a Lewis acid.

If desired, the reaction of 4-(oxiraneylmethoxy)-9H-carbazole, a compound of formula 2 with N-2-[2'-(methoxy)-phenoxy]-ethyl]-benzylamine, a compound of formula 5 in an aprotic organic solvent in presence of catalytic amount of an acid compound to obtain 1-[N-{benzyl}-2'-({2''-(methoxy)phenoxy)-ethyl}-amino]-3-[9'''H-carbazol-4'''-yloxy]-propan-2-ol, a compound of formula 6 may be carried out in one solvent and the subsequent denbenzylation of compound of formula 6 to obtain compound of formula 1 may be carried out in another solvent.

In a preferred embodiment of the process of the present invention, the aprotic organic solvent for step 'a' of the process is ethyl acetate and the debenzylation reaction is carried out in presence of Pd/C catalyst in ethyl acetate, characterized in that the ratio of 4-(oxiraneylmethoxy)-9H-carbazole:Pd/C catalyst is 1:0.14 wt/wt.

Example

To (450 ml) of ethyl acetate, 4-(oxiraneylmethoxy)-9H-carbazole (25g, 0.1 moles) and N-2-[2'-(methoxy)-phenoxy]-ethyl]-benzylamine (80.6g, 0.31 moles) was added under stirring at room temperature, followed by catalytic amount of acetic acid (~1.5 ml). The reaction mixture was heated to 76-78°C and maintained for 24 hours. Additional 4-(oxiraneylmethoxy)-9H-carbazole (25g, 0.1 moles) and catalytic amount of acetic acid (~1.5 ml) was added and reaction mixture was refluxed for 24 hours. The reaction mixture was cooled, transferred to hydrogenator and (7g) of wet Pd/C catalyst (5% Pd content and 50% moisture content) was added. The nitrogen gas was purged into the hydrogenator and evacuated under vacuum, followed by purging with hydrogen gas up to 4-4.5 Kg/cm^2. The reaction mixture was heated to about 60-65°C and maintained under 4.5 Kg/cm^2 hydrogen pressure at about 65-70°C for about 8-12 hours. The reaction mixture was filtered and filtrate was concentrated under vacuum at about 40-45°C to distill out ethyl acetate completely. (Alternately, ethyl acetate can be concentrated and left for crystallization) To the residue, (100ml) butanol was added and stirred for about 10-12 hours. The resultant crude 1-[9'H-carbazol-4'-yloxy]-3-[{2''-(2''-(methoxy)phenoxy)-ethyl}-amino]-propan-2-ol was isolated by filtration at about 20-25°C and washed with (50ml) butanol, followed by (50ml) toluene. Yield is about 44-50 g.

Purification: To (50g) crude 1-[9'H-carbazol-4'-yloxy]-3-[{2''-(2''-(methoxy)phenoxy)-ethyl}-amino]-propan-2-ol, about 150-200ml of ethyl acetate was added under stirring. The reaction mixture was heated to about 70-75°C and stirred for 30 minutes to obtain a clear solution. Which was charcolised with (2.5g) charcoal. The resultant hot solution was filtered through hyflo bed and gradually cooled to about 20-22°C and stirred at 20-22°C for about 2 to about 3 hours. The resultant 1-[9'H-carbazol-4'-yloxy]-3-[{2''-(2''-

(methoxy)phenoxy)-ethyl}-amino]-propan-2-ol was isolated by filtration and suck dried. The yield is about 33-38 g.

Dated this 20th day of June 2003.

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LIMITED